REMARKS

Reconsideration is requested.

Claims 1-8, 11-14, 19-21, 23, 24, 27-34 and 36-53 are pending. Claims 29-34 and 36 have been allowed. Claims 37-53 have been added. Support for the new claims may be found throughout the specification. Claim 2 has been re-written in independent form, without prejudice, to advance prosecution. Claims 37-53 are similar to claims 3-8, 11-14, 19-21, 23, 24, 27 and 28, but for being directly or indirectly dependent from claim 2. No new matter has been added.

Claim 1 has been revised to refer to "C_{16} to C_{18}" as appears to be the more often granted alternative claim language of the U.S. Patent Office. Specifically, the applicants note that the following four (4) U.S. patents have issued since 1976 with the claim recitation of "C16-C18 fatty acid":

Refine Search | ACLM/"C16-C18 fatty acid"

	PAT. NO.	Title
1	6,491,746	Protective coating
2	6,238,723	Edible fat spread
3	5,750,663	Solid soap/syndet composition
4	5,324,455	Process for preparing a high bulk density detergent composition having improved dispensing properties

The following 13 U.S. Patents issued since 1976 contain the recitation of "C16-C18 fatty acid" in some aspect of the on-line searchable fields:

Refine Search | "C16-C18 fatty acid"

	PAT. NO.	Title
1	7,312,184	Recovery composition and method
2	7,255,808	Functional fluid compositions containing erosion inhibitors
3	6,965,043	Process for making high purity fatty acid lower alkyl esters
4	6,869,922	Cleaning formulation
5	6,776,234	Recovery composition and method
6	6,491,746	Protective coating
7	6,255,265	Low synthetic soap bars comprising organic salts and polyalkylene glycol
8	6,238,723	Edible fat spread
9	6,143,704	Soap bars with little or no synthetic surfactant comprising organic salts
10	5,750,663	Solid soap/syndet composition
11	5,456,800	System for sizing paper and cardboard
12	5,324,455	Process for preparing a high bulk density detergent composition having improved dispensing properties
13	5,246,603	Fragrance microcapsules for fabric conditioning

The following seven (7) U.S. Patents have been granted since 1976 with a claim containing the phrase “C16 to C18 fatty acid” :

Refine Search | ACLM/"C16 to C18 fatty acid"

	PAT. NO.	Title
1	7,156,912	Colored composition
2	6,491,746	Protective coating
3	6,346,236	Sunscreens from vegetable oil and plant phenols
4	6,238,723	Edible fat spread
5	5,985,817	Pourable, thickened aqueous bleach and abrasive containing compositions
6	5,750,663	Solid soap/syndet composition
7	5,324,455	Process for preparing a high bulk density detergent composition having improved dispensing propertie

Finally, the following 34 U.S. Patents have issued since 1976 containing the phrase “C_{16} to C_{18} fatty acid” in the claims:

Refine Search | ACLM/"C.sub.16 to C.sub.18 fatty acid"

	PAT. NO.	Title
1	7,408,087	Process for making unsaturated coconut and/or palm nut fatty alcohols
2	6,998,371	Nail polish remover comprising fatty acid ester and alkyl lactate
3	6,923,838	Fuel additive composition and method for treatment of middle distillate fuels and gasoline
4	6,869,922	Cleaning formulation
5	6,428,794	Lotion composition for treating tissue paper
6	6,231,687	Lubrication treatment method for cold working of steel
7	RE37,101	Stabilized phosphate ester-based functional fluid compositions
8	6,028,067	Cyclosporin-containing microemulsion preconcentrate composition
9	5,908,654	Triglycerides rich in polyunsaturated fatty acids
10	5,716,692	Lotioned tissue paper
11	5,637,743	Quaternary ammonium surfactants derived from tertiary amines and fabric softeners containing quaternary ammonium surfactants
12	5,530,137	Methods and compositions for stabilizing fatty acid imidazoline solutions
13	5,464,551	Stabilized phosphate ester-based functional fluid compositions
14	5,427,614	Starch based formulations
15	5,244,954	Moulding thermoplastic compositions endowed with improved mould release characteristics
16	5,200,433	Process for preparing low density porous crosslinked polymeric materials
17	4,876,107	Substitute milk fat compositions
18	4,820,448	Surfactant mixtures and their use
19	4,746,505	Technetium radiodiagnostic fatty acids derived from bisamide bisthiol ligands
20	4,673,727	Novel poly(ester-amide) compositions
21	4,668,438	Aqueous concentrates of salts of .alpha.-sulfonated fatty acid alkyl esters
22	4,655,780	Encapsulated bleach particles coated with a mixture of C.sub.16 -C.sub.18 and C.sub.12 -C.sub.14 fatty acid soaps
23	4,610,889	Low-trans fats and oil- and water emulsion spreads containing such fats
24	4,568,556	Margarine product and process
25	4,447,462	Structural fat and method for making same
26	4,425,371	Margarine fat blend
27	4,390,561	Margarine oil product
28	4,388,339	Margarine and method for making same
29	4,290,965	Method of making 1.sup.123 labeled fatty acids
30	4,234,498	Preparation of glyceride esters

31 4,220,562 T Laundry additive product
32 3,962,467 T Processes of drying yeast
33 3,959,495 T Reconstitution of dry yeast in dough preparation
34 3,948,829 T Strippable, thin, protective coating

The claims have been revised, without prejudice, to recite the range of fatty acids of the unamended claims in a form which appears to be preferred by the U.S. Patent Office. While the claims and specifications of the above-noted patents have not been reviewed in detail, the above is believed to be evidence that the unamended claims are definite in that one of ordinary skill will appreciate that the recitation "C16-C18 fatty acid" of the specification will be recognized by one of ordinary skill in the art.

The applicants further note that unamended claims 3, 27 and 28 define specific cofactors which are not indefinite for the stated reasons.

Withdrawal of the Section 112, second paragraph, rejection of claims 1-8, 11-14, 19-21, 23, 24, 27 and 28 is requested. Claim 2, and new claims 37-53 dependent therefrom, do not include the objected-to phrase. The claims are submitted to be definite.

The Section 112, first paragraph "written description", rejection of claims 1-8, 11-14, 19-21, 23, 24, 27 and 28 stated on pages 4-5 of the Office Action dated August 11, 2008 is traversed. Reconsideration and withdrawal of the rejection are requested in view of the above and the following comments.

The rejection is understood to include a rejection of the recitation of "C16-18" as allegedly constituting new matter ("Further, the cofactor represented in claim 1 as C16-

C18 constitutes a new matter because such structure representing fatty acids were not presented in the original disclosure.") and a rejection based on the recitation of "with at least one double bond in the cis configuration" as allegedly also constituting new matter.

As noted above, the claims have been revised in a manner which obviates the new matter objection based on the previous recitation of "C16-C18".

With regard to the objection to the recitation of "at least one double bond in the cis configuration", the applicants note that claim 2 is supported by an adequate written description as same is not dependent on claim 1, which was the stated basis for the rejection of same. See page 5 of the Office Action dated August 11, 2008. Moreover, claim 3 defines the cofactor of claim 1 as cis C18:1:11 fatty acid and claim 27 defines the cofactor of claim 1 as being an unsaturated fatty acid selected from the group of: C18:1:11cis , C18:1:6cis, C18:2:9,12cis, C16:1:9cis, C18:3:6,9,12cis and C18:3:9,12,15cis. Claim 28 further defines the cofactor as being selected from the group of: C18:1:11cis , C18:1:6cis, C18:3:6,9,12cis and C18:3:9,12,15cis. The Examples of the specification demonstrate the specific complexes of the claims effectively induce cell death in L1210 cells, for example. Claims 3, 27 and 28 therefore further defines the number of double bonds in the cis configuration. Claims 2, 3, 27 and 28, and claims dependent therefrom, therefore are supported by an adequate written description.

As for the recitation of claim 1, the applicants believe that one of ordinary skill in the art will appreciate from the application as filed that the applicants were in possession of the claimed invention at the time the application was filed. Specifically,

the applicants note that the examples of the specification, describe cofactors of the invention containing three (3) double bonds in the cis configuration. See for example, Figure 3 of the specification. The specification further describes the following general relationship relating structure of the cofactor to the function of the claimed invention, for example, on page 12:

> In HAMLET, α-lactalbumin retains a partially unfolded conformation as well as a high affinity Ca^{2+} binding site. This apparent paradox sheds new light on the molecular characteristics of α-lactalbumin in the complex. The X-ray structure of the native like apo form shows that the alpha and beta regions are largely intact, while the cleft between them is widened (Chrysina et al., J. Biol. Chem, (2000) 275, 37021-9). As discussed above, the applicants believe that the cofactor such as oleic acid binds in the interface between the alpha and the beta domains, and that the bound cofactor acid locks this region of the molecule, while allowing the .alpha.-domain to maintain a native-like conformation. This is supported by the finding illustrated hereinafter that complexes of this type such as HAMLET binds Ca^{2+} while retaining activity against tumor cells. It would appear therefore that HAMLET is therefore in a different molecular state than either the low salt apo α-lactalbumin or the native-like apo form in physiological salt.

The general nature of the interaction and relationship of the alpha-lactalbumin and cofactor of the claimed invention is further described, for example, in the following passage spanning pages 24-25 of the specification:

> The shape of the hydrophobic pocket suggested that it should favour interactions with bent molecules (Fig. 1). This may indeed explain the inability of the C18:1 trans conformers to form HAMLET. While fatty acids in this cis conformation are u-shaped around the double bond, with both carbon chains projecting in one direction, trans fatty acids are rod shaped around the double bond due to the carbon chains on opposite sides of the double bond. The saturated fatty acids are most flexible with no structural

> constraints due to the lack of double bonds. The results thus indicate that only the cis conformation allows fatty acids a close stereo-specific fit, and that the additional critical feature of the fatty acid is the carbon chain length. In addition, the pocket is capped by basic residues, which may co-ordinate the polar head groups of the fatty acids, thus orienting the lipid. This interaction is, however not sufficient for activation as the trans and saturated fatty acids, which possess the same charged head group failed to form the active complex. It is highly likely that the stereo specific fit involves both hydrophobic interactions with the lipid tail and electrostatic interactions of the negatively charged head group with basic side chains. Based on the analogy with other fatty acid binding proteins, the fatty acid may bind to HAMLET by electrostatic interactions between its negatively charged head group and basic side-chains in the protein, as well as by van der Waal's contacts and hydrophobic effects with the tail that are optimized with the preferred stereo specific match (C18:1:9cis).

Further, the originally filed claims provided the following description of the disclosed invention (emphasis added):

> 1. A biologically active complex comprising alpha-lactalbumin or a variant of alpha-lactalbumin (α-lactalbumin) which is in the apo folding state, or a fragment of either of any of these, and a cofactor which stabilises the complex in a biologically active form, provided that any fragment of α-lactalbumin or a variant thereof comprises a region corresponding to the region of α- lactalbumin which forms the interface between the alpha and beta domains, and further provided that when the complex comprises native a-lactalbumin, the cofactor is other than C18:1: 9 cis fatty acid.
>
> 2. A complex according to claim 1 wherein the cofactor is a cis C18:1: 9 or C18:1:11 fatty acid or a different fatty acid with a similar configuration.
>
> 3. A biologically active complex according to claim 1 which is obtainable by combining (i) a cis C18:1:9 or C18:1:11 fatty acid or a different fatty acid with a similar configuration ; and (ii) α-lactalbumin from which calcium ions have been removed, or a variant of α-lactalbumin from which calcium

> ions have been removed or which does not have a functional calcium binding site ; or a fragment of either of any of these, provided that any fragment comprises, a region corresponding to the region of α- lactalbumin which forms the interface between the alpha and beta domains, and further provided that when (ii) is alpha- lactalbumin, (i) is other than C18:1:9 cis fatty acid.

One of ordinary skill in the art will appreciate, such as from the attached references of Kozakai et al ("Isolation and Structural Elucidation of Hemolysin from the Phytoflagellate *Prymnesium parvum*" Agric Biol. Chem., 46(1), 233-236 (1982)) and Ishihara et al. ("Purification of Stearidonic Acid (18:4(n-3)) and Hexadecatetraenoic Acid (16:4(n-3)) from Algal Fatty Acid with Lipase and Medium Pressure Liquid Chromatography" Biosci. Biotechnol. Biochem., 64 (11), 2454-2457, 2000) that unsaturated C_{16} and C_{18} fatty acids with 4 and 5 double bonds were known at the time of the present invention.

The applicants submit that the specification provides an adequate written description of the claimed invention which recites the cofactor as being an unsaturated C_{16} to C_{18} fatty acid with at least one double bond in the cis configuration.

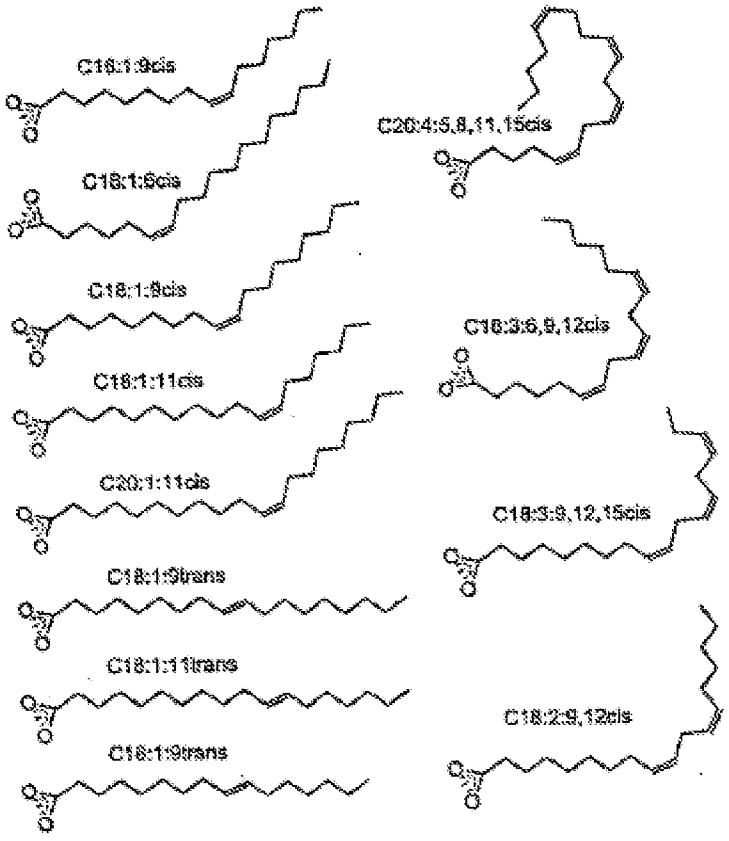
Withdrawal of the Section 112, first paragraph "written description", rejection of claims 1-8, 11-14, 19-21, 23, 24, 27 and 28 stated on pages 4-5 of the Office Action dated August 11, 2008 is requested.

The Section 112, first paragraph "written description" rejection of claims 1-8, 11-14, 19-21, 23, 24, 27 and 28 stated on pages 5-6 of the Office Action dated August 11, 2008 is traversed. Reconsideration and withdrawal of the rejection are requested in view of the above and the following.

The basis of the rejection is understood to be as follows:

> The instant specification discloses different examples where the only effective fatty acid that activates native lactalbumin to its active HAMLET form is oleic acid, for example. The disclosure does not pint out specifically which other fatty acids in the range of structure containing 16 or 17 or 18 carbons would be as effective.

The applicants respectfully disagree with the Examiner's characterization of the evidence of the specification. While working examples are not required to support the claims of a patent, the applicants note that the present specification describes the following cofactors in Figure 1:



and provides the results in Figure 3 of the viability of L1210 cells after exposure to converted material and free fatty acids involving the following cofactors (see also pages 18-19 of the specification):

18:1: 9c (HAMLET)
18:1: 9tr
18:1:11c
18:1:6c
18:3 c
γ18:3 c
18:1 :11tr
18:2 c

16:1:9c
16:1 :9tr

20:1:11c
20:4 c

Moreover, the above-described passages of the specification provide a description of the structure-function relationship between the protein and cofactor of the claimed invention. Contrary to the assertion of the Examiner therefore, the applicants have described a sufficient number of species as well as a general description of the claimed invention to demonstrate the applicants were in possession of the claimed invention at the time the application was filed.

Withdrawal of the Section 112, first paragraph "written description", rejection of claims 1-8, 11-14, 19-21, 23, 24, 27 and 28 stated on pages 5-6 of the Office Action dated August 11, 2008 is requested.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested. The Examiner is requested to contact the undersigned, preferably by telephone, in the event anything further is required.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: /B. J. Sadoff/
B. J. Sadoff
Reg. No. 36,663

BJS:
901 North Glebe Road, 11th Floor
Arlington, VA 22203-1808
Telephone: (703) 816-4000
Facsimile: (703) 816-4100